II. Amendments to the Specification

The priority information in the cross-reference to related applications has been amended to correct various typographical inconsistencies within the paragraph, as well as update the status of the priority information.

The Glossary material inserted into the specification has been reproduced verbatim (except for correction of two spelling mistakes and the addition of a Series Number) from pp. 10-15 of U.S.S.N. 07/492,462 (now U.S. 5,143,854) to which priority is claimed and which is incorporated by reference (see Cross-Reference to Related Applications at p.1 of the present specification). The material is copied into the present specification for ease of reference, and does not affect the merits (see MPEP 2163.07(b)).

No new matter is added by these amendments.

III. Amendments to the Claims

Applicants have amended Claim 172 to change the term "known locations" to "positionally defined locations". Applicants have amended Claims 183, 185, 186, and 189-192 to change the term "predefined region" to "positionally defined location". Applicants have amended Claims 205 and 206 to change the term "preselected regions" to "positionally defined locations". Support for these amendments can be found throughout the specification, for example, at page 4, lines 5-8.

Applicants have amended Claims 172 and 193 to change the term "different polypeptides" to "polypeptides, which differ in composition." Claim 183 has been amended to change the term "different" to "different in composition." Support for this amendment can be found, for example, on page 186, line 15 to page 188, line 9, where the syntheses of four polypeptides differing in composition is taught.

Applicants have amended Claim 172 to clarify that a functional group in a first and second selectively activated region is attached to the substrate, a linker, an amino acid coupled to the substrate, an amino acid coupled to a linker that is attached to the substrate, a nascent polypeptide coupled to a linker, and/or a nascent polypeptide coupled to the substrate. Support for the amendment can be found at page 9, paragraph 1, page 49, line 14 to page 50, line 31; page 57, line 23 to page 58, line 20; page 59, lines 1 to 15; and page 59, line 28 to page 60, line 9 of

the specification. Applicants have also amended Claim 172 to clarify that a protecting group has been removed from said second selectively activated region of the surface without removing protecting groups from other positionally defined locations of the substrate. Support for this amendment can be found, for example, on page 145, line 25 to page 146, line 2 of the specification. These amendments to Claim 172 are non-limiting, and are made for clarification purposes only.

Applicants have amended Claims 185, 187, 188, and 189 to correct the antecedent basis for the phrase "steps of irradiating".

Applicants have amended Claim 195 for clarity.

No new matter has been added.

IV. Priority Applications

The Examiner has requested that Applicants clarify the applications to which priority has been claimed. For the Examiner's convenience, Applicants have included a diagrammatic representation of the chain of priority of the instant application in Exhibit A. U.S.S.N. 09/557,875, the parent of the instant application is a continuation-in-part of U.S.S.N. 08/348,471 and a continuation of U.S.S.N. 09/056,927 (now U.S. 6,197,506). Both U.S.S.N. 08/348,471 and U.S.S.N. 09/056,927 belong to the same patent family and claim priority back to U.S.S.N. 07/362,901 (now abandoned). U.S.S.N. 08/348,471 is a continuation of U.S.S.N. 07/805,727 (now U.S. 5,424,186), which is a continuation-in-part of U.S.S.N. 07/624,120 (now abandoned), which is a continuation-in-part of U.S.S.N. 07/492,462 (now U.S. 5,143,854), which is a continuation-in-part of 07/362,901 (now abandoned). U.S.S.N. 09/056,927 (now 6,197,506), which is a continuation of U.S.S.N. 08/670,118 (now U.S. 5,800,992), which is a divisional of U.S.S.N. 08/168,904 (now abandoned), which is a continuation of U.S.S.N. 07/624,114 (now abandoned). U.S.S.N. 07/624,114 is a continuation-in-part of both U.S.S.N. 07/492,462 (now U.S. 5,143,854) and U.S.S.N. 07/362,901 (now abandoned).

The Examiner has additionally requested that Applicants update the current status of the parent applications. Parent applications that have had a change in status include U.S.S.N. 09/056,927 (now U.S. 6,197,506), U.S.S.N. 08/168,904 (now abandoned), U.S.S.N. 07/624,120 (now abandoned), U.S.S.N. 07/624,114 (now abandoned), and U.S.S.N. 07/362,901 (now

abandoned). The first paragraph of the application has been amended to reflect these status changes.

V. Formal Drawings

Formal Drawings for the present application were mailed to the U.S. Patent and Trademark Office on October 4, 2001. A copy of the date-stamped postcard receipt is enclosed. Duplicate Formal Drawings can be provided upon request.

VI. Rejection of Claims 172-184, 186, and 188-192 Under 35 U.S.C. § 112, First Paragraph for Lack of Written Description

A. Summary of the Rejection

The Examiner states that Claim 172-184, 186, and 188-192 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Examiner states that the specification is directed to the use of photolithographic techniques in methods of making arrays of chemical compounds. However, the Examiner states that the specification does not provide a description for the open-ended method of synthesizing a polypeptide array in the instant claims.

B. Argument

Among other factors, the instant claims are based in part on the inventive concept that polymers can be synthesized by combinatorial methods by the selective application of an activating agent, which will remove protecting groups and subsequently allow growth of a polymer on specific regions of a substrate. Although the methods are largely exemplified by the use of a mask to direct light to specific regions of a substrate, where it removes photosensitive protecting groups, the specification clearly teaches that other activating agents and protecting groups can be employed in a similar manner. At page 63, line 33 through page 64, line 6 of the specification, there is a listing of activating agents other than light, including electron beam irradiation, x-ray irradiation, electric current and electric field (see also U.S. Patent No. 6,379,895). In addition, the specification lists other activating agents such as magnetic fields (see page 19, line 38 through page 20, line 6), chemical agents (e.g., acids, see page 21, lines 7-

28), heat (see page 133, lines 26-38), laser pumping (see page 133, lines 26-38), and oxidation and reduction with microelectrodes (see page 133, lines 26-38).

The use of activating agents other than light, along with appropriate protecting groups, for synthesis of a single peptide species on a solid support were well-known in the art at the time of invention. For example, electrolysis was known to remove the protecting group TROC (2,2,2-trichloroethyloxycarbonyl), which is well-suited for use in oligonucleotide and peptide synthesis (see Semmelhack *et al.*, *J. Am. Chem. Soc.* 94, 5139 (1972) (reference WG) and Van Hijfte and Little, *J. Org. Chem.* 50, 3940 (1985) (reference XG)). The trityl protecting group and the 4-nitrobenzyl-oxycarbonyl protecting group can also be electrochemically removed (see Vairanovsky, *Angew. Chem. Int. Ed. Engl.* 15, 281 (1976)). The t-butoxycarbonyl (t-BOC) is both chemically and thermally labile. Its use and chemical removal are discussed in the present application at page 21, lines 7-28. Geysen (see WO 86/00991) has also reported the use of t-BOC as a chemical protecting group with respect to his methods for the simultaneous synthesis of multiple peptide chain. Also, it was known by 1988 that t-BOC could be thermally removed during the preparation of polypeptides (see Munegumi *et al.*, *Chem. Lett.* 10, 1643 (1988)(reference UG)).

Strategies for the selective removal of protecting groups, such as the protecting groups discussed immediately above, are analogous to those employed for the removal of photosensitive groups. For example, t-BOC can be chemically, thermally, or electrochemically removed by first juxtaposing a substrate with a physical barrier that has holes. In a chemical removal process, the barrier forms a water- or solvent-tight seal with the substrate. Such a barrier is depicted, for example in Figure 11 of U.S. 5,547,839, "Sequence of Surface Immobilized Polymer Utilizing Microfluorescence Detection," by William J. Dower and Stephen P. A. Fodor ("Exhibit B"), which is incorporated by reference on page 1, line 31 of the specification. Subsequent immersion of the substrate in an acid solution selectively activates regions through holes in the barrier. For thermal removal, the barrier blocks certain regions of the substrate from absorbing radiation. Heat can be delivered using, for example, a laser beam by essentially the same strategy as in photodeprotection. For electrodeprotection, a nonconducting barrier can be used in the removal of electrochemical groups. Immersion of the substrate in an electrolyte and applying an electric field deprotects those regions not covered by the barrier.

Other general strategies for the selective removal of protecting groups are disclosed at page 10, lines 6-9 of the specification, where it states that "[d]ifferential reaction is achieved by selectively exposing reactive functional groups to, e.g., light, electric currents, or another spatially localized activator." Examples include electro-optical and optical methods, similar to many of the processes used in semiconductor wafer and chip fabrication (see page 17, line 38 to page 18, line 2). Other examples include x-ray and electron beam lithography, where the beams can be focused on a particular region of a substrate (see page 29, lines 28 to 35). Protecting groups comprising a sulfonyl moiety are particularly appropriate for electron beam lithography.

Alternatively, deprotection by chemical or some electrical methods can be achieved by the surface topography of a substrate. The specification at page 26, lines 1-5, teaches that the substrate and its surface preferably form a rigid support on which to carry out reactions, and such reactions can take place on raised or depressed regions of the substrate. Item 8 of the glossary (see page 5 of the instant amendment) teaches that it may be desirable to physically separate synthesis regions for different polymers. The specification at page 26, lines 18-26, further teaches that the surface of the substrate can be physically divided, or etched, using well known techniques to provide surface features such as trenches, v-grooves, and mesa structures. One skilled in the art would recognize that trenches in a surface allow one to selectively flow a protecting agent or a deprotecting agent (including electrolyte solutions and electric current) into a selected region of a substrate, thereby selectively activating said trenches.

Applicants' specification discloses several methods of selectively protecting and deprotecting peptides bound to a particular region of a substrate. Applicants have further demonstrated that activating agents other than light were well-known in the art at the time of the instant application's effective filing date. Therefore, Applicants' specification provides sufficient written description of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

VII. Rejection of Claims 172-184, 186, and 188-192 under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

A. Summary of the Rejection

The Examiner states that the specification is enabling for photolithographic methods in protection and deprotection steps of the present method. However, the Examiner believes that the specification does not provide enablement for the use of other techniques such as chemical or magnetic methods. The Examiner specifically states that there is insufficient enabling disclosure for the use of chemical, thermal, or magnetic techniques to remove the protecting groups from the compounds, so that an activated region on the substrate surface is formed. Also, the Examiner states that the prior art at the time the invention was made was such that synthesis of an array of compounds on a substrate by selectively protecting and deprotecting using chemical or magnetic methods was difficult or unknown. The Examiner reasons that selectively protecting or deprotecting compounds using chemical or thermal methods is not possible without using other methods such as masking using barriers.

B. Argument

As discussed above, examples of the use of chemical, thermal, and magnetic methods in protecting and deprotecting compounds as part of synthesizing a *single* polypeptide species (i.e., *not* a selective synthesis) on a solid support were known at the time of the invention was made. As the Examiner has acknowledged, Applicants have disclosed how to *selectively* protect and deprotect regions of a substrate using photolithographic methods. The specification additionally teaches chemical, thermal, and electrical methods of *selectively* deprotecting regions of a substrate, which are largely analogous to the photolithographic methods.

In one example, the masks taught in the photolithographic methods are analogous to a solvent-tight barrier (e.g., for chemical and electrochemical methods). An example of an appropriate solvent-tight barrier can be found in U.S. 5,547,839 (hereinafter "Exhibit B"), which is incorporated by reference on page 1, line 31 of the specification. Figure 11 of Exhibit B shows a schematic diagram of a reactor chamber formed by a substrate being sealed to an apparatus comprising entry and exit points for reagents. One skilled in the art would recognize the use of a

reaction chamber having a smaller surface area than the substrate, such that one could position the chamber to selectively activate regions of the substrate.

In another example, several of the disclosed deprotection methods use a beam that can be focused onto a specific region of a substrate, thereby deprotecting a selected area and eliminating the need for a mask. Such deprotection methods include x-ray and electron beam lithography (see page 29, lines 28 to 35) and laser methods for thermal deprotection (see page 133, lines 26-38).

In yet another example, selective deprotection of a region of the substrate by chemical or some electrical methods is achieved by the surface topography of a substrate. The specification at page 26, lines 3-5, teaches that the substrate and its surface preferably form a rigid support on which to carry out reactions. Item 8 of the glossary (see page 5 of the instant amendment) teaches that it may be desirable to physically separate synthesis regions, such as by using wells, raised regions, or etched trenches. The specification at page 26, lines 18-26, further teaches that the surface of the substrate can be physically separated, or etched, using well known techniques to provide surface features such as trenches, v-grooves, and mesa structures. One skilled in the art would recognize that trenches in a surface allow one to selectively flow a protecting agent or a deprotecting agent (including electrolyte solutions and electric current) into a discrete, selected region of a substrate.

Given the teachings of the instant application regarding selectively activating a region of a substrate, a person skilled in the art would be able to prepare a peptide array using activators other than light. Therefore, one skilled in the art would be able to practice the claimed invention without undue experimentation. Reconsideration and withdrawal of the rejection are respectfully requested.

VIII. Rejection of Claims 172-184, 186, and 188-192 Under 35 U.S.C. § 112, Second Paragraph as Being Incomplete for Omitting Essential Elements

A. Summary of the Rejection

The Examiner states that Claim 172-184, 186, and 188-192 omit essential elements, leading to a gap between the elements. In particular, the Examiner states that the claims do not recite how the first selectively activated region or second activated regions are formed.

B. Argument

Applicants respectfully submit that the instant claims do not omit an essential element. Claim 172, as amended, for example, recites that a first protected amino acid is selectively coupled to a functional group in a first selectively activated region of a surface. Thus, it is inherent in the claim language that the first and the second selectively activated regions of the surface must be activated (e.g., deprotected). The specification teaches at page 19, lines 33-38, that selective activation is achieved as follows:

> The regions which define particular reagents will usually be generated by selective protecting groups which may be activated or deactivated. Typically the protecting group will be bound to a monomer subunit or spatial region, and can be spatially affected by an activator, such as electromagnetic radiation.

Moreover, as discussed above in Section V, the specification teaches several methods of activating select regions of the substrate (see, for example, page 63, line 33 through page 64, line 6; page 19, line 38 through page 20, line 6; page 21, lines 7-28; and page 133, lines 26-38). Since Applicants have demonstrated that there are several methods of activating select regions of the substrate, it is unreasonable to require that Applicants specify one particular method in a claim. Given the teachings of Applicants' specification, one skilled in the art would immediately recognize that one of the above-named methods could be used to activate a select region of the substrate, and thus the instant claims sufficiently describe the subject matter claimed by Applicants. Reconsideration and withdrawal of the rejection are respectfully requested.

IX. Rejection of Claims 172, 174-182, and 190-209 Under 35 U.S.C. § 112, Second Paragraph As Being Indefinite

A. Summary of the Rejection

The Examiner states Claims 172, 174-182, and 190-209 are indefinite because they recite the phrase "different polypeptides." The Examiner states that it is not clear how the polypeptides are different, whether by length or by amino acid composition.

B. Argument

Applicants have amended independent Claims 172, 183, and 193 to recite "polypeptides, which differ in composition". The amendment clarifies how polypeptides of the peptide array differ. Support for this amendment can be found, for example, on page 186, line 15 to page 188, line 9, where the syntheses of four polypeptides differing in composition is taught. This amendment is non-limiting and made for clarification purposes only. Reconsideration and withdrawal of the rejection are respectfully requested.

X. Rejection of Claims 185, 187, 188, and 189 Under 35 U.S.C. § 112, Second Paragraph

A. Summary of the Rejection

The Examiner states there is insufficient antecedent basis for the phrase "said step(s) of irradiating" in Claims 185, 187, 188, and 189.

B. Argument

Applicants have amended the instant claims to recite "irradiation step(s)", which finds proper antecedent basis in Claim 184, which recites "step of removing is an irradiation step." The instant claims all depend on Claim 184. Reconsideration and withdrawal of the rejection are respectfully requested.

XI. Rejection of Claim 194 Under 35 U.S.C. § 112, Second Paragraph

A. Summary of the Rejection

The Examiner states that the meaning of "combinations thereof" in Claim 194 is not clear.

B. Argument

One skilled in the art would recognize which combinations of substrate materials are reasonable. It is well-known, for example, that materials such as silicon nitride and silicon dioxide can be grown on silicon (see page 1, first paragraph of the website www.phys.ttu.edu/~mholtz/Silicon.html, "Exhibit C"). Similar combinations can be made for

the other substrate materials recited in the claim. For example, one skilled in the art would immediately recognize that it is possible to combine polystyrene and silicon oxide by layering one over the other. Reconsideration and withdrawal of the rejection are respectfully requested.

XII. Rejection of Claim 195 Under 35 U.S.C. § 112, Second Paragraph

A. Summary of the Rejection

The Examiner states that Claim 195 is indefinite by reciting the phrase "and mixtures thereof." The Examiner states that it is not clear to what the phrase refers.

B. Argument

Applicants maintain that the phrase "and mixtures thereof", in reference to a recitation of protecting groups is clear as written. Applicants note that the protecting groups recited by Claim 195 can each only form one bond; consequently, it is impossible for a mixture of the recited protecting groups to be combined into a larger protecting group. However, as the Examiner suggests, it is chemically feasible for amino acids in one area of the substrate to be protected by one type of protecting group and the other area to be protected by a different protecting group.

To expedite prosecution, Applicants have amended Claim 195 to recite that a protective group is *one or more* protective groups selected from the group consisting of 6-nitroveratryloxycarbonyl, 2-nitrobenzyloxy carbonyl, dimethyl dimethoxybenzyloxy carbonyl, 5-bromo-7-nitroindolinyl, o-hydroxyalpha-methyl cinnamoyl, and 2-oxymethylene anthriquinone. This amendment is made for clarification that more than one protecting group may be present in a polypeptide array, and is not limiting in any way. Reconsideration and withdrawal of the rejection are respectfully requested.

XIII. Rejection of Claim 172-209 Under Obviousness-Type Double Patenting Over U.S. Patent Nos. 5,405,783, 5,143,854, 5,384,261, and 6,329,143

A. U.S. Patent Nos. 5,405,783, 5,384,261, and 6,329,143

The Examiner has rejected the instant application over U.S. Patent Nos. 5,405,783 ("the '783 Patent"), 5,384,261 ("the '261 Patent), and 6,329,143 ("the '143 Patent").

Applicants enclose herewith a Terminal Disclaimer in which the owner, of U.S. Patent Nos. 5,405,783, 5,384,261, and 6,329,143, Affymetrix, Inc., disclaims the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 of the '783, '261, and '143 Patents.

In the discussion of the '783 Patent, the Examiner states that the instant array of polypeptides could not have been prepared using other types of protecting groups. Applicants object to the Examiner's statement . As discussed above in Section VI, the present application discloses numerous types of protecting groups and methods of deprotection that can be used to prepare peptide arrays of the invention.

B. U.S. Patent No. 5,143,854 ("the '854 Patent")

The Examiner states that the present claims conflict with claims 1-13 of the '854 Patent. The Examiner acknowledges that the claims are not identical, but the Examiner states that the claims are not patentably distinct from each other because the method of identifying a polypeptide in the '854 Patent includes a method of synthesis of a polypeptide array on a substrate.

The subject matter of the '854 Patent was previously divided in a Restriction Requirement (a copy is provided as Exhibit D). In the Restriction Requirement, the claims of Group II, drawn to a method of screening sequences on a solid support, were elected, and subsequently issued as the '854 Patent. Group I, drawn to a method of preparing sequences on a solid support, was not elected and rights to prosecution of these claims were preserved by filing a series of continuing applications. 35 U.S.C. §121 states:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

Based on the previous Restriction Requirement, the Patent Office has determined that the claims of the '854 Patent (Group II) and the claims of the subject application (Group I) are patentably distinct inventions. Withdrawal of the double patenting rejection is respectfully requested.

XIV. Provisional Rejection of Claim 172-209 Under Obviousness-Type Double Patenting Over U.S. Patent Application No. 08/563,759

The Examiner has provisionally rejected the instant application over Application Serial No. 08/563,759 (the '759" application).

MPEP §804 clarifies how provisional double patenting rejections of copending applications are to be handled by the Examiner (Page 800-19).

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Applicants respectfully request that the Examiner proceed in accordance with MPEP §804 as cited.

XV. Applications Claiming Related Subject Matter

The Examiner has requested that Applicants supply a listing of applications claiming related subject matter, in order to identify *potential* double patenting issues. Related pending applications include: U.S. Serial Nos. 08/456,887, 08/563,759, 09/057,162, 09/063,933, 09/465,126, 09/557,875, 09/614,068, 09/653,761, 09/654,206, 09/654,435, 09/946,605, and 10/033,195. In addition, U.S. Patent No. 6,346,413 has issued since the Office Action dated December 18, 2001.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the first paragraph at page 1 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The present application is a continuation of U.S.S.N. 09/557,875 filed April 24, 2000, which is a continuation of U.S.S.N. 09/056,927 filed April 8, 1998 (now U.S. 6,197,506), which is a continuation of U.S.S.N. 08/670,118 filed June 25, 1996[,] (now U.S. [Patent No.]5,800,992), which is a divisional of U.S.S.N. 08/168,904 filed December 15, 1993 (now abandoned), which is a continuation of U.S.S.N. 07/624,114, filed December 6, 1990 (now abandoned) (all incorporated by reference), which is a continuation-in-part of commonly assigned patent applications Pirrung *et al.*, U.S.S.N. 07/362,901 (VLSIPS parent) filed on June 7, 1989 (now abandoned); and Pirrung *et al.*, U.S.S.N. 07/492,462 (VLSIPS CIP), filed on March 7, 1990 (now U.S. 5,143,854), which are hereby incorporated herein by reference. U.S.S.N. 09/557,875, [The present application] filed April 24, 2000, is also a continuation-in-part of U.S.S.N. 08/348,471 filed November 30, 1994, which is a continuation of [USSN] U.S.S.N. 07/805,727 filed December 6, 1991 (now U.S. [Patent No.] 5,424,186), which is a continuation-in-part of [USSN] U.S.S.N. 07/624,120, filed December 6, 1990 (now abandoned), which is a continuation-in-part of [USSN] U.S.S.N. 07/492,462, filed March 7, 1990 (now U.S. [Patent No.] 5,143,854), which is a continuation-in-part of [USSN] U.S.S.N. 07/362,901, filed June 7, 1989 (now abandoned). Additional commonly assigned applications Barrett *et al.*, U.S.S.N. 07/435,316 (caged biotin parent) filed November 13, 1989; and Barrett *et al.*, U.S.S.N. 07/612,671 (caged biotin CIP), filed November 13, 1990 are also incorporated herein by reference. Additional applications Pirrung *et al.*, U.S.S.N. 07/624,120 (now abandoned) a divisional of which has issued as [US] U.S. 5,744,101 and Dower *et al.*, U.S.S.N. 07/626,730 (now [US] U.S. 5,547,839), which are also commonly assigned and filed on the same day as this application, are also hereby incorporated herein by reference.

Add the following paragraphs at page 13, line 30:

Glossary

The following terms are intended to have the following general meanings as they are used herein:

1. Complementary: Refers to the topological compatibility or matching together of interacting surfaces of a ligand molecule and its receptor. Thus, the receptor and its ligand can be described as complementary, and furthermore, the contact surface characteristics are complementary to each other.

2. Epitope: The portion of an antigen molecule which is delineated by the area of interaction with the subclass of receptors known as antibodies.

3. Ligand: A ligand is a molecule that is recognized by a particular receptor. Examples of ligands that can be investigated by this invention include, but are not restricted to, agonists and antagonists for cell membrane receptors, toxins and venoms, viral epitopes, hormones (e.g., opiates, steroids, etc.), hormone receptors, peptides, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligonucleotides, nucleic acids, oligosaccharides, proteins, and monoclonal antibodies.

4. Monomer: A member of the set of small molecules which can be joined together to form a polymer. The set of monomers includes but is not restricted to, for example, the set of common L-amino acids, the set of D-amino acids, the set of synthetic amino acids, the set of nucleotides and the set of pentoses and hexoses. As used herein, monomers refers to any member of a basis set for synthesis of a polymer. For example, dimers of L-amino acids form a basis set of 400 monomers for synthesis of polypeptides. Different basis sets of monomers may be used at successive steps in the synthesis of a polymer.

5. Peptide: A polymer in which the monomers are alpha amino acids and which are joined together through amide bonds and alternatively referred to as a polypeptide. In the context of

this specification it should be appreciated that the amino acids may be the L-optical isomer or the D-optical isomer. Peptides are more than two amino acid monomers long, and often more than 20 amino acid monomers long. Standard abbreviations for amino acids are used (e.g., P for proline). These abbreviations are included in Stryer, Biochemistry, Third Ed., 1988, which is incorporated herein by reference for all purposes.

6. Radiation: Energy which may be selectively applied including energy having a wavelength of between 10^{-14} and 10^{4} meters including, for example, electron beam radiation, gamma radiation, x-ray radiation, ultra-violet radiation, visible light, infrared radiation, microwave radiation, and radio waves. "Irradiation" refers to the application of radiation to a surface.

7. Receptor: A molecule that has an affinity for a given ligand. Receptors may be naturally-occurring or manmade molecules. Also, they can be employed in their unaltered state or as aggregates with other species. Receptors may be attached, covalently or noncovalently, to a binding member, either directly or via a specific binding substance. Examples of receptors which can be employed by this invention include, but are not restricted to, antibodies, cell membrane receptors, monoclonal antibodies and antisera reactive with specific antigenic determinants (such as on viruses, cells or other materials), drugs, polynucleotides, nucleic acids, peptides, cofactors, lectins, sugars, polysaccharides, cells, cellular membranes, and organelles. Receptors are sometimes referred to in the art as anti-ligands. As the term receptors is used herein, no difference in meaning is intended. A "Ligand Receptor Pair" is formed when two macromolecules have combined through molecular recognition to form a complex.

Other examples of receptors which can be investigated by this invention include but are not restricted to:

a) Microorganism receptors: Determination of ligands which bind to receptors, such as specific transport proteins or enzymes essential to survival of microorganisms, is useful in a new class of antibiotics. Of particular value would be antibiotics against opportunistic fungi, protozoa, and those bacteria resistant to the antibiotics in current use.

b) Enzymes: For instance, the binding site of enzymes such as the enzymes responsible for cleaving neurotransmitters; determination of ligands which bind to certain receptors to modulate the action of the enzymes which cleave the different neurotransmitters is useful in the development of drugs which can be used in the treatment of disorders of neurotransmission.

c) Antibodies: For instance, the invention may be useful in investigating the ligand-binding site on the antibody molecule which combines with the epitope of an antigen of interest; determining a sequence that mimics an antigenic epitope may lead to the development of vaccines of which the immunogen is based on one or more of such sequences or lead to the development of related diagnostic agents or compounds useful in therapeutic treatments such as for autoimmune diseases (e.g., by blocking the binding of the "self" antibodies).

d) Nucleic Acids: Sequences of nucleic acids may be synthesized to establish DNA or RNA binding sequences.

e) Catalytic Polypeptides: Polymers, preferably polypeptides, which are capable of promoting a chemical reaction involving the conversion of one or more reactants to one or more products. Such polypeptides generally include a binding site specific for at least one reactant or reaction intermediate and an active functionality proximate to the binding site, which functionality is capable of chemically modifying the bound reactant. Catalytic polypeptides are described in, for example, U.S. application Serial No. 07/404,920, which is incorporated herein by reference for all purposes.

f) Hormone receptors: For instance, the receptors for insulin and growth hormone. Determination of the ligands which bind with high affinity to a receptor is useful in the development of, for example, an oral replacement of the daily injections which diabetics must take to relieve the symptoms of diabetes, and in the other case, a replacement for the scarce human growth hormone which can only be obtained from cadavers or by recombinant DNA technology. Other examples are the vasoconstrictive hormone receptors; determination of those ligands which bind to a receptor may lead to the development of drugs to control blood pressure.

g) Opiate receptors: Determination of ligands which bind to the opiate receptors in the brain is useful in the development of less-addictive replacements for morphine and related drugs.

8. Substrate: A material having a rigid or semi-rigid surface. In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different polymers with, for example, wells, raised regions, etched trenches, or the like. According to other embodiments, small beads may be provided on the surface which may be released upon completion of the synthesis.

9. Protective Group: A material which is bound to a monomer unit and which may be spatially removed upon selective exposure to an activator such as electromagnetic radiation. Examples of protective groups with utility herein include Nitroveratryloxy carbonyl, Nitrobenzyloxy carbonyl, Dimethyl dimethoxybenzyloxy carbonyl, 5-Bromo-7-nitroindolinyl, *o*-Hydroxy-α-methyl cinnamoyl, and 2-Oxymethylene anthraquinone. Other examples of activators include ion beams, electric fields, magnetic fields, electron beams, x-ray, and the like.

10. Predefined Region: A predefined region is a localized area on a surface which is, was, or is intended to be activated for formation of a polymer. The predefined region may have any convenient shape, e.g., circular, rectangular, elliptical, wedge-shaped, etc. For the sake of brevity herein, "predefined regions" are sometimes referred to simply as "regions."

11. Substantially Pure: A polymer is considered to be "substantially pure" within a predefined region of a substrate when it exhibits characteristics that distinguish it from other predefined regions. Typically, purity will be measured in terms of biological activity or function as a result of uniform sequence. Such characteristics will typically be measured by way of binding with a selected ligand or receptor.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

172. (Amended) A method of synthesizing a polypeptide array, wherein said array comprises at least two [different] polypeptides, which differ in composition, immobilized on a substrate[, and wherein said polypeptides are synthesized on a surface of said substrate], said method comprising:

(a) contacting [said] a surface of the substrate with a first protected amino acid wherein said first protected amino acid is selectively coupled to a functional group selected from the group consisting of:

(i) a functional group attached to the substrate;

(ii) a functional group attached to a linker that is attached to the substrate;

(iii) a functional group attached to an amino acid that is coupled to the substrate;

(iv) a functional group attached to an amino acid that is coupled to a linker that is attached to the substrate;

(v) a functional group attached to a nascent polypeptide that is coupled to a linker that is attached to the substrate;

(vi) a functional group attached to a nascent polypeptide coupled to the substrate; and

(vii) combinations thereof,

wherein the functional group is in a first selectively activated region of said surface, and wherein a protecting group has been removed from said first selectively activated region of the surface without removing protecting groups from other positionally defined locations of the substrate;

(b) contacting said surface with a second protected amino acid wherein said second protected amino acid is selectively coupled to a functional group selected from the group consisting of:

(i) a functional group attached to the substrate;

(ii) a functional group attached to a linker that is attached to the substrate;

(iii) a functional group attached to an amino acid that is coupled to the substrate;

(iv) a functional group attached to an amino acid that is coupled to a linker that is attached to the substrate;

(v) a functional group attached to a nascent polypeptide that is coupled to a linker that is attached to the substrate;

(vi) a functional group attached to a nascent polypeptide coupled to the substrate; and

(vii) combinations therof,

wherein the functional group is in a second selectively activated region of said surface, and wherein a protecting group has been removed from said second selectively activated region of the surface without removing protecting groups from other positionally defined locations of the substrate; and,

(c) repeating the above steps until at least two [different] polypeptides, which differ in composition, are formed at [known] positionally defined locations on said substrate surface.

183. (Amended) A method for synthesizing polypeptides on a substrate, said method comprising:

a) providing a substrate wherein said substrate comprises immobilized polypeptide molecules, said polypeptide molecules coupled to a removable protecting group[s];

b) removing said protecting group from said polypeptide molecules in a first [predefined region] positionally defined location of said substrate without removing said protecting groups from a second [predefined region] positionally defined location of said substrate; and

c) contacting said substrate with a first amino acid to couple said first amino acid to said polypeptide molecules in said first [predefined region] positionally defined location, said first amino acid having an amino acid protecting group thereon, forming a first polypeptide on said substrate in said [first predefined region] positionally defined location that is different in composition from a[n] polypeptide in said second [predefined region] positionally defined location.

185. (Amended) The method as recited in claim 184, wherein said irradiation step [of irradiating] is a step of masking a light source with a mask placed between said light source and said substrate, said mask comprising first transparent regions and second opaque regions, said transparent regions transmitting light from said source to at least said first [predefined region] positionally defined location, and said opaque regions blocking light from said source to at least said second [predefined region] positionally defined location.

186. (Amended) The method as recited in claim 183, wherein said first and second [regions] positionally defined location each have total areas less than about 1 cm^2.

187. The method as recited in claim 184, wherein said irradiation steps [of irradiating] are conducted with a monochromatic light.

188. The method as recited in claim 184, wherein said irradiation steps [of irradiating] and contacting are repeated so as to synthesize 10^3 different polypeptides on said substrate.

189. (Amended) The method as recited in claim 184, wherein the irradiation step [of irradiating] for a first [predefined region] positionally defined location is a step of irradiating half of a [region] positionally defined location of said substrate irradiated in a prior synthesis step, and not irradiating half of said [region] positionally defined location irradiated in a prior synthesis step.

190. (Amended) The method as recited in claim 183, wherein said steps a) and b) are repeated to synthesize more than 1,000 different polypeptides on different synthesis [regions] locations of said substrate, each of said different polypeptides occupying an area of less than about 10^{-2} cm^2 to about $1x10^{-5}$ cm^2.

191. (Amended) The method as recited in claim 190, wherein said steps a) and b) are repeated to synthesize more than 1,000 different polypeptides on different synthesis [regions] locations

surface defined by the patterns of light and dark areas formed during the irradiating steps and the amino acids coupled in said contacting steps.

195. (Amended) The method as recited in claim 193, wherein said protective group is one or more protective groups selected from the group consisting of 6-nitroveratryloxycarbonyl, 2-nitrobenzyloxy carbonyl, dimethyl dimethoxybenzyloxy carbonyl, 5-bromo-7-nitroindolinyl, o-hydroxyalpha-methyl cinnamoyl, and 2-oxymethylene anthriquinone[, and mixtures thereof].

205. (Amended) The method as recited in claim 204, wherein said additional steps are performed so as to synthesize 10^3 different polypeptides in 10^3 respective [preselected regions] positionally defined locations on said substrate.

206. (Amended) The method as recited in claim 204, wherein said additional steps are performed so as to synthesize 10^6 different polypeptides in 10^6 respective [preselected regions] positionally defined locations on said substrate.

of said substrate, each of said different polypeptides occupying an area of less than about 10^{-2} cm^2 to about $1x10^{-4}$ cm^2.

192. (Amended) The method as recited in claim 191, wherein said steps a) and b) are repeated to synthesize more than 1,000 different polypeptides on different synthesis [regions] <u>locations</u> of said substrate, each of said different polypeptides occupying an area of less than about 10^{-2} cm^2 to about $1x10^{-3}$ cm^2.

193. (Amended) A method of synthesizing polypeptides, said method comprising:

a) generating a pattern of light and dark areas by selectively irradiating at least a first area of a surface of a substrate, said surface comprising immobilized amino acids on said surface, said amino acids coupled to a photoremovable protective group, without irradiating at least a second area of said surface, to remove said protective group from said amino acids in said first area;

b) simultaneously contacting said first area and said second area of said surface with a first amino acid to couple said first amino acid to said immobilized amino acids in said first area, and not in said second area, said first amino acid having said photoremovable protective group;

c) generating another pattern of light and dark areas by selectively irradiating with light at least a part of said first area of said surface and at least a part of said second area to remove said protective group in said at least a part of said first area and said at least a part of said second area;

d) simultaneously contacting said first area and said second area of said surface with a second amino acid to couple said second amino acid to said immobilized amino acids in at least a part of said first area and at least a part of said second area; and

e) performing additional irradiating and amino acid contacting and coupling steps so that a matrix array of at least 100 [different] polypeptides<u>, which differ in composition,</u> is formed on said surface, each different polypeptide synthesized in an area of less than 0.1 cm^2, whereby said different polypeptides have sequences and locations on said

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157; In re Hawkins, 486 F.2d 579, 179 USPQ 163; In re Hawkins, 486 F.2d 577, 179 USPQ 167.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5, 8-14, 16-25, 28-35, 37-39, 42 and 43, drawn to a method of preparing sequences on a solid support, classified in Class 530, subclass 334.

II. Claims 6, 7, 15, 26, 27, 36, 40, 41, 44-54, and 75, drawn to a method of screening sequences on a solid support, classified in Class 436, subclass 518.

III. Claims 55-68 and 76-104, drawn to an apparatus for preparing a plurality of polymers, classified in Class 422, subclass 131.

IV. Claims 69-74, drawn to a substrate for screening for biological activity, classified in Class 436, subclass 518.

V. Claim 105, drawn to a method of synthesizing an RNA or DNA binding sequence for sequencing by hybridization, classified in Class 536, subclass 27.

Inventions of Group I and Groups III and IV are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (M.P.E.P. § 806.05(e)). In this case the process as claimed can be practiced by another materially different apparatus, and the apparatuses of Groups III and IV can be used to practice other and materially different processes. The apparatus of Group III does not have the specificity of the process of Group I and could therefore be used to prepare surfaces involving several surfaces of the same polymer, or surfaces involving more than two monomers, and the process of Group I as claimed could involve activators other than energy sources, such as chemical activators. The substrate of Group IV is materially different than the process of Group I because it does not include language specifying selective exposure of parts of its surface to first and second monomers, and further states a specific number of ligands immobilized on its surface. Thus, the apparatus of Group IV is not required to practice the process of Group I, and the

process of Group I is not required to prepare the apparatus of Group IV.

The inventions of Group III and Group IV are related as distinct apparatuses. According to MPEP 803, there are two criteria for restriction between patentably distinct inventions:

1. the inventions must be independent or distinct as claimed; and
2. there must be serious burden on the examiner if restriction is not required.

The apparatuses of Group III and Group IV are independent of one another as:

1. The apparatus of Group III does not require the specific number of immobilized ligands of Group IV; and
2. The apparatus of Group IV does not require the selective activation of the apparatus of Group III.

Inventions of Group II and Groups III and IV are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (M.P.E.P. § 806.05(e)). In this case the process as claimed can be practiced by a materially different apparatus which does not involve the specific number of ligands immobilized on its surface

as claimed in Group IV or is prepared by methods differing from those of Groups III and V as illustrated, supra.

Inventions of Group V and Groups III and IV are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (M.P.E.P. § 806.05(e)). In this case the process as claimed can be practiced by another materially different process. The apparatuses of Groups III and IV as claimed do not include nucleic acids. The process of Group V also does not include the limitations of the apparatuses of Groups III or IV.

The inventions of Group I, Group II and Group V are related as distinct processes. According to MPEP 803, there are two criteria for restriction between patentably distinct inventions:

1. the inventions must be independent or distinct as claimed; and
2. there must be serious burden on the examiner if restriction is not required.

The processes of Group I, Group II and Group V are independent of one another as:

1. The process of Group I is drawn to a method of preparation, whereas the method of Group II is drawn to a method of

detection. The process of Group I as claimed does not require the screening process of Group II;

2. The process of Group I does not include the nucleic acids of Group V and can be practiced with activators other than photochemical.

Because these inventions are distinct for the reasons given above and have achieved separate status in the art as shown by their different classification and/or their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Vern Norviel on March 8, 1991, a provisional election was made without traverse to prosecute the invention of Group II, claims 6, 7, 15, 26, 27, 36, 40, 41, 44-54, and 75. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-5, 8-14, 16-25, 28-35, 37-39, 42, 43, 55-74, and 76-105 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition